

What Is Claimed Is:

1. A combination comprising a first amount of
5 an aldosterone receptor antagonist and a second amount
of a beta-adrenergic antagonist, wherein said
aldosterone receptor antagonist and beta-adrenergic
antagonist together comprise a therapeutically-effective
amount of said aldosterone receptor antagonist and said
10 beta-adrenergic antagonist.

2. The combination of Claim 1 wherein said
aldosterone receptor antagonist is selected from epoxy-
containing compounds.

3. The combination of Claim 2 wherein said
epoxy-containing compound has an epoxy moiety fused to
the "C" ring of the steroidal nucleus of a 20-spiroxane
compound.

4. The combination of Claim 3 wherein said
20-spiroxane compound is characterized by the presence
of a 9a-,11a-substituted epoxy moiety.

5. The combination of Claim 2 wherein said
epoxy-containing compound is selected from the group
consisting of:

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo,g-lactone, methyl ester, (7a,11a,17a)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo-dimethyl ester, (7a,11a,17a)-;

3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid,
9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-
lactone, (6b,7b,11b,17b)-;

FOI 2007-047660

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester, monopotassium salt, (7a,11a,17a)-;

5

pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7a,11a,17a)-;

10

3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, g-lactone (6a,7a,11.a)-;

15

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)-;

20

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6a,7a,11a,17a)-;

25

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, g-lactone, (6a,7a,11a.,17a)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, g-lactone, ethyl ester, (7a,11a,17a)-; and

30

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, g-lactone, 1-methylethyl ester, (7a,11a,17a)-.

35 6. The combination of Claim 4 wherein said epoxy-steroidal-type compound is eplerenone.

7. The combination of Claim 6 wherein said beta-adrenergic antagonist is selected from the group

0917403-072701
FOZ220" E0H4T660

consisting of acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, bevantolol, bisoprolol, bopindolol, bucumolol, bucindolol, bunitrolol, butofilolol, carteolol, carvedilol, celiprolol, 5 cloranolol, indenolol, labetalol, levoprolol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol, nifenalol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, topol, and viskenit.

10 8. The combination of Claim 6 wherein said beta-adrenergic antagonist is selected from the group consisting of Acc 9369, AMO-140, betaxolol, capsinolol, carazolol, CP-331684, diprafenone, ersentilide, esmolol, esprolol, Fr-172516, ISV-208, L-653328, laniolol, 15 levobunolol, LM-2616, nipradilol, Pharmaprojects No 5279, S-atenolol, SB-226552, SR-58894A, SR-59230A. talinolol, tertatolol, tilisolol, TZC-5665, UK-1745, xamoterol, and YM-430.

20 9. The combination of Claim 7 further characterized by said beta-adrenergic antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about one-to-twenty of 25 said beta-adrenergic antagonist to said aldosterone receptor antagonist.

10. The combination of Claim 9 wherein said weight ratio range is from about one-to-five to about 30 one-to-fifteen.

11. The combination of Claim 10 wherein said weight ratio range is about one-to-ten.

09047403 072704
T02240 CON T660

12. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises carvedilol or a pharmaceutically-acceptable salt thereof.

5 13. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises metoprolol or a pharmaceutically-acceptable salt thereof.

10 14. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises bisoprolol or a pharmaceutically-acceptable salt thereof.

15 15. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises bucindolol or a pharmaceutically-acceptable salt thereof.

20 16. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises propranolol or a pharmaceutically-acceptable salt thereof.

17. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises esmolol or a pharmaceutically-acceptable salt thereof.

25 18. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises acebutolol or a pharmaceutically-acceptable salt thereof.

30 19. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises sotalol or a pharmaceutically-acceptable salt thereof.

35 20. The combination of Claim 6 wherein the beta-adrenergic antagonist comprises labetalol or a pharmaceutically-acceptable salt thereof.

09917403-072701
10/22/03 04:16:50

21. The combination of Claim 1 wherein said aldosterone antagonist is spironolactone.

22. The combination of Claim 21 wherein
5 said beta-adrenergic antagonist is selected from the group consisting of acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, bevantolol, bisoprolol, bopindolol, bucumolol, bucindolol, bunitrolol, butofilolol, carteolol, carvedilol, celiprolol,
10 cloranolol, indenolol, labetalol, levoprolol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol, nifenalol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, toprol, and viskenit.

23. The combination of Claim 21 wherein said
15 beta-adrenergic antagonist is selected from the group consisting of Acc 9369, AMO-140, betaxolol, capsinolol, carazolol, CP-331684, diprafenone, ersentilide, esmolol, esprolol, Fr-172516, ISV-208, L-653328, laniolol,
20 levobunolol, LM-2616, nipradilol, Pharmaprojects No 5279, S-atenolol, SB-226552, SR-58894A, SR-59230A. talinolol, tertatolol, tilisolol, TZC-5665, UK-1745, xamoterol, and YM-430.

24. The combination of Claim 22 further
25 characterized by said beta-adrenergic antagonist and said aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about one-to-twenty of said beta-adrenergic
30 antagonist to said aldosterone receptor antagonist.

25. The combination of Claim 24 wherein said weight ratio range is from about one-to-five to about one-to-fifteen.

26. The combination of Claim 25 wherein said weight ratio range is about one-to-ten.

27. The combination of Claim 21 wherein the
5 beta-adrenergic antagonist comprises carvedilol or a pharmaceutically-acceptable salt thereof.

28. The combination of Claim 21 wherein the
10 beta-adrenergic antagonist comprises metoprolol or a pharmaceutically-acceptable salt thereof.

29. The combination of Claim 21 wherein the
15 beta-adrenergic antagonist comprises bisoprolol or a pharmaceutically-acceptable salt thereof.

30. The combination of Claim 21 wherein the
beta-adrenergic antagonist comprises bucindolol or a pharmaceutically-acceptable salt thereof.

31. The combination of Claim 21 wherein the
20 beta-adrenergic antagonist comprises propranolol or a pharmaceutically-acceptable salt thereof.

32. The combination of Claim 21 wherein the
25 beta-adrenergic antagonist comprises esmolol or a pharmaceutically-acceptable salt thereof.

33. The combination of Claim 21 wherein the
30 beta-adrenergic antagonist comprises acebutolol or a pharmaceutically-acceptable salt thereof.

34. The combination of Claim 21 wherein the
35 beta-adrenergic antagonist comprises sotalol or a pharmaceutically-acceptable salt thereof.

09917403-072701

35. The combination of Claim 21 wherein the beta-adrenergic antagonist comprises labetalol or a pharmaceutically-acceptable salt thereof.

5 36. The combination of Claim 1 wherein said beta-adrenergic antagonist is selected from the group consisting of acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, bevantolol, bisoprolol, bopindolol, bucumolol, bucindolol, bunitrolol, 10 butofilolol, carteolol, carvedilol, celiprolol, cloranolol, indenolol, labetalol, levoprolol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol, nifenalol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, toprol, and viskenit.

15 37. The combination of Claim 1 wherein said beta-adrenergic antagonist is selected from the group consisting of Acc 9369, AMO-140, betaxolol, capsinolol, carazolol, CP-331684, diprafenone, ersentilide, esmolol, 20 esprolol, Fr-172516, ISV-208, L-653328, laniolol, levobunolol, LM-2616, nipradilol, Pharmaprojects No 5279, S-atenolol, SB-226552, SR-58894A, SR-59230A, talinolol, tertatolol, tilisolol, TZC-5665, UK-1745, xamoterol, and YM-430.

25 38. The combination of Claim 36 wherein said aldosterone receptor antagonist is eplerenone.

30 39. The combination of Claim 37 wherein said aldosterone receptor antagonist is eplerenone.

40. The combination of Claim 36 wherein said aldosterone receptor antagonist is spironolactone.

35 41. The combination of Claim 37 wherein said aldosterone receptor antagonist is spironolactone.

0947403-072701

42. A pharmaceutical composition comprising a first amount of an aldosterone receptor antagonist and a second amount of a beta-adrenergic antagonist, wherein
5 said aldosterone receptor antagonist and beta-adrenergic antagonist together comprise a therapeutically-effective amount of said aldosterone receptor antagonist and said beta-adrenergic antagonist.

10 43. The pharmaceutical composition of Claim 42 wherein said aldosterone receptor antagonist is selected from epoxy-containing compounds.

15 44. The pharmaceutical composition of Claim 43 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane compound.

20 45. The pharmaceutical composition of Claim 44 wherein said 20-spiroxane compound is characterized by the presence of a 9a-,11a-substituted epoxy moiety.

25 46. The pharmaceutical composition of Claim 45 wherein said epoxy-steroidal-type compound is eplerenone.

30 47. The pharmaceutical composition of Claim 42 wherein said aldosterone receptor antagonist is spironolactone.

35 48. A therapeutic method for treating a cardiovascular disorder, said method comprising administering to a subject susceptible to or afflicted with such disorder a first amount of an aldosterone receptor antagonist and a second amount of a beta-adrenergic antagonist, wherein said aldosterone receptor

09017403-072701

antagonist and beta-adrenergic antagonist together comprise a therapeutically-effective amount of said aldosterone receptor antagonist and said beta-adrenergic antagonist.

5

49. The method of Claim 48, wherein said cardiovascular disorder is selected from the group consisting of hypertension, congestive heart failure, cirrhosis and ascites.

10

50. The method of Claim 49, wherein said cardiovascular disorder is hypertension.

15

51. The method of Claim 49, wherein said cardiovascular disorder is congestive heart failure.

09947403.07E204